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<b>(21) International Application Number:</b> PCT/US96/04239  <b>(22) International Filing Date:</b> 27 March 1996 (27.03.96)  <b>(30) Priority Data:</b> 95200771.4 28 March 1995 (28.03.95) EP <b>(34) Countries for which the regional or international application was filed:</b> AT et al.  <b>(71) Applicant (for all designated States except US):</b> MALLINCKRODT MEDICAL, INC. [US/US]; 675 McDonnell Boulevard, P.O. Box 5840, St. Louis, MO 63134 (US).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> JOHANNSEN, Bernd [DE/DE]; Lausitzer Strasse 5, D-01324 Dresden (DE). PIETZSCH, Hans-Juergen [DE/DE]; Kaethe-Kollwitz-Strasse 5, D-01809 Heidenau (DE). SCHEUNEMANN, Matthias [DE/DE]; Wiemkenhofsweg 33, D-26125 Oldenburg (DE). SPIES, Harmut [DE/DE]; Racknitzhohe 49, D-01217 Dresden (DE). BRUST, Peter [DE/DE]; Heinrichsweg 9, D-38889 Blankenburg (DE).  <b>(74) Agent:</b> MCBRIDE, Thomas, P.; Mallinckrodt Medical, Inc., 675 McDonnell Boulevard, P.O. Box 5840, St. Louis, MO 63134 (US).		<b>(81) Designated States:</b> CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> <sup>99m</sup> Tc - LABELLED SEROTONIN RECEPTOR BINDING SUBSTANCES  <b>(57) Abstract</b>  <p>The invention relates to a zero-charged <sup>99m</sup>Tc - labelled substance having a serotonin receptor binding activity, wherein the serotonin receptor binding compound is represented by the general formula (I): L - A - B - E, wherein L is a chelating moiety selected from the group consisting of a tridentate/monodentate chelating combination; A is a 2- to 8-membered hydrocarbon biradical, wherein the carbon atoms may be interrupted by one or two heteroatoms selected from O and S; B is an N-(C<sub>1</sub>-C<sub>4</sub>) alkyl group, an NH group, or an optionally substituted piperidin-derived, piperazin-derived, morpholin-derived or pyrrolidin-derived biradical; and E is an aryl or heteroaryl group or wherein E together with B constitutes an optionally substituted 2,4-dihydroquinazolyl group; wherein said serotonin receptor binding compound is labelled with technetium-<sup>99m</sup> in the form of oxotechnetium (V), said technetium being attached to said compound by means of said chelating moiety. The invention also relates to a method of preparation of said labelled substance, a radiopharmaceutical composition comprising said labelled substance, a method for detecting and localizing tissues having serotonin receptors with the aid of said labelled substance and a kit for preparing a radiopharmaceutical composition containing said labelled substance.</p>		

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<sup>99m</sup>Tc - labelled serotonin receptor binding substances

The present invention relates to zero-charged <sup>99m</sup>Tc - labelled substances having a serotonin receptor binding activity, to a method of preparing these substances, to radiopharmaceutical compositions comprising these substances, to the use of these compositions for imaging purposes, and to a kit for preparing a radiopharmaceutical composition.

Studying serotonin receptors, particularly the 5-HT<sub>2</sub> receptors, in brain is of interest because of the importance of altered serotonergic neurotransmission in many neurological and psychological diseases and disorders. It was suggested from animal and human studies that serotonin receptors are involved in aging, sleep, pain, temperature control, Alzheimer disease, schizophrenia, eating disorders, anxiety, depression and suicide. PET and SPECT imaging may significantly improve our understanding of the physiology and pathophysiology of these processes and disorders and may contribute to new approaches for treatment of neurological and psychological diseases and disorders. Therefore the development of suitable radiolabelled substances for imaging serotonin receptors in brain is important.

There are three main groups of 5-HT receptors, namely 5-HT<sub>1</sub>, 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors, which are further divided into several subtypes. Among the 5-HT<sub>2</sub> receptors only the 5-HT<sub>2A</sub> (previously named 5-HT<sub>2</sub>) and the 5-HT<sub>2C</sub> receptors (previously named 5-HT<sub>1C</sub>) are present in the brain in significant amounts. For Positron Emission Tomography (PET) a number of serotonin receptor imaging agents are already available, such as [<sup>11</sup>C]ketanserin (Berridge et al., J. Lab. Compds. Radiopharm. 1983, 20, 73-78), N-[<sup>11</sup>C-methyl]ketanserin (Frost et al., J. Nucl. Med. 1987, 28 (Suppl.), 600), and [<sup>18</sup>F]altanserin (Lemaire et al., J. Nucl. Med., 1991, 32, 2266-2272). To allow a broad clinical application, however, the development of serotonin receptor imaging agents for the imaging technique of Single Photon Emission Computed Tomography (SPECT) is required. Aiming at such SPECT tracers, ketanserin (Mertens et al., WO90/11093) and certain 5-HT<sub>1A</sub> receptor antagonists, such as 4-(2'-methoxyphenyl)-1-[2'-(N-(2"-pyperidinyl)-p-iodobenzamido)ethyl]-piperazine (p-MPPI) and related compounds (Zhuang et al., J. Med. Chem.,

1994, 37, 1406-1407) have been labelled with  $^{123}\text{I}$ .

$^{123}\text{I}$ , however, is not the radionuclide of choice for imaging purposes, because this isotope has the main disadvantage of being not readily available in the hospital (no generator nuclide and a relatively short half-life). The most suitable radionuclides are metal-radionuclides, in particular the generator nuclide  $^{99\text{m}}\text{Tc}$ , having an optimum half-life and superior radiation characteristics. Therefore a  $^{99\text{m}}\text{Tc}$  - labelled substance for serotonin receptor imaging is by far the preferred agent for diagnosing certain neurological and psychological diseases and disorders. Ballinger et al. (Appl. Radiat. Isot., 1989, 40, 547-549) have prepared  $^{99\text{m}}\text{Tc}$  - labelled spiperone dithiocarbamate as a potential radiopharmaceutical for dopamine receptor imaging with SPECT. Biodistribution studies, however, showed a low uptake of radioactivity in the brain. Nanjappan et al. (IXth. Intern. Symp. on Radiopharm. Chem., 1992, 69; Paper B9) have described  $^{99\text{m}}\text{Tc}$  - labelled 3-quinuclidinyl benzylate boronic acid complexes (QNB-BATO's) as potential muscarine acetylcholinergic receptor (mAChR) tracers. Changes in mAChR density in the brain have been associated with several neurodegenerative disorders such as Alzheimer disease. The QNB-BATO stereoisomers (the synthesis results in four different stereoisomers), however, showed high non-specific binding affinity, which makes these complexes not suitable for imaging purposes in practice. Recently, Lever et al. (Nucl. Med. Biol., 1994, 21, 157-164) have investigated related  $^{99\text{m}}\text{Tc}$  - labelled compounds for mAChR imaging. The observed affinity for the target receptors, however, was also insufficient for clinical application as mACh receptor tracers. Finally, very recently Kung et al. (J. Nucl. Biol. Med., 1994, 38, 449-450) have disclosed some new  $^{99\text{m}}\text{Tc}$  -  $\text{N}_2\text{S}_2$ -complexes as potential  $5\text{HT}_{1\text{A}}$  receptor imaging agents, based upon the above-described p-MPPI as the substrate. Unfortunately, however, the  $^{99\text{m}}\text{Tc}$ -p-MPP prepared did not display any brain activity in vivo experiments.

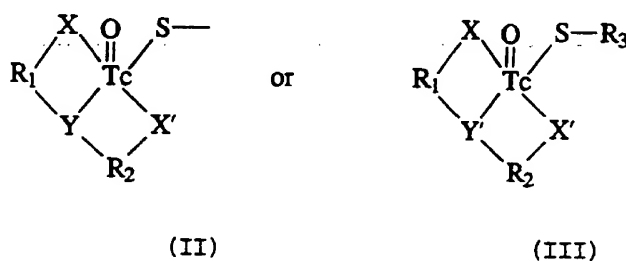
It is the objective of the present invention to provide  $^{99\text{m}}\text{Tc}$  - labelled substances having a high and selective binding affinity to serotonin receptors, in particular to  $5\text{-HT}_{2\text{A}}$  receptors, which make them promising for imaging of serotonin receptor related processes, in particular neurological and psychological diseases and disorders.

This objective can be achieved, according to the present invention, by a zero-charged  $^{99m}\text{Tc}$  - labelled substance having a serotonin receptor binding activity, wherein the serotonin receptor binding compound is represented by the general formula



wherein:

L is a metal labelled chelating moiety with the general formula



wherein:

X and X' are each individually O or S;

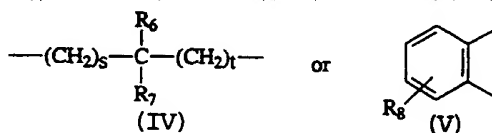
Y is O, S, Se,  $\text{NR}_4$ ,  $\text{PR}_4$  or  $-\text{C}(\text{R}_4)=\text{N}-$ ,

wherein  $\text{R}_4$  is a hydrogen atom or a  $(\text{C}_1-\text{C}_6)$ alkyl group, optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, oxo, [N-mono- or N,N-di $(\text{C}_1-\text{C}_3)$ alkyl]-amino,  $(\text{C}_1-\text{C}_3)$ alkyl,  $(\text{C}_1-\text{C}_3)$ alkoxy and optionally substituted phenyl;

Y' is  $\text{NR}_4'$  or  $\text{PR}_4'$  or  $-\text{C}(\text{R}_4')=\text{N}-$ ,

wherein  $\text{R}_4'$  is a covalent bond to A;

$\text{R}_1$  and  $\text{R}_2$  are each independently a biradical of the general formula



wherein:

$\text{R}_6$ ,  $\text{R}_7$  or  $\text{R}_8$  are each individually selected from the group consisting of hydrogen,  $(\text{C}_1-\text{C}_3)$ alkyl,  $(\text{C}_1-\text{C}_3)$ alkoxy and fluoro, or wherein  $\text{R}_6$  and  $\text{R}_7$  together

constitute an oxo group; and

s and t are each individually 0, 1 or 2, with the proviso that s and t together are 1 or 2;

R<sub>3</sub> is a substituent selected from the group consisting of substituted or unsubstituted (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, and phenyl, wherein the substituents are selected from the group consisting of (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, halogen and trifluoromethyl;

Tc is <sup>99m</sup>Tc;

A is a 2- to 8-membered hydrocarbon biradical, wherein the carbon atoms may be interrupted by one or two heteroatoms selected from O and S;

B is an N-(C<sub>1</sub>-C<sub>4</sub>)alkyl group, an NH group, or an optionally substituted piperidin-derived, piperazin-derived, morpholin-derived or pyrrolidin-derived biradical; and

E is selected from the following groups:

Ar-C(=T)<sub>r</sub>-(CH<sub>2</sub>)<sub>p</sub>-, Ar-O-(CH<sub>2</sub>)<sub>q</sub>-, Ar-S-(CH<sub>2</sub>)<sub>q</sub>-, Ar-C(Ar')-C(=T)<sub>r</sub>-(CH<sub>2</sub>)<sub>p</sub>- and Ar-C(Ar')=,

wherein:

p is an integer from 0 to 4;

q is an integer from 0 to 3;

r is an integer from 0 to 1;

T is O or H<sub>2</sub>; and

Ar and Ar' are each independently unsubstituted or substituted aryl or heteroaryl groups, wherein the aryl or heteroaryl groups are selected from phenyl, pyridyl, pyrrolyl, triazinyl, pyridazinyl, imidazolyl, pyrazolyl, pyrazinyl, pyrimidinyl, indolyl, isoindolyl, indazolyl, benzofuranyl and benzisoxazolyl, and wherein the substituents are selected from halogen, trifluoromethyl, (C<sub>1</sub>-C<sub>4</sub>)alkyl and (C<sub>1</sub>-C<sub>4</sub>)alkoxy;

or wherein E together with B constitutes an optionally substituted 2,4-dihydroquinazolyl group attached with its (3-N) atom to A.

Suitable substituents of the piperidin, piperazin, morpholin or

pyrrolidin moiety are halogen, (C<sub>1</sub>-C<sub>3</sub>)alkyl and (C<sub>1</sub>-C<sub>3</sub>)alkoxy.

The essential features of the invention, which make the labelled substances promising for the intended purpose, are:

- 5 - neutral or zero-charged <sup>99m</sup>Tc - labelled substances to improve their transport through the blood-brain barrier;
- the coupling of a group E, having a serotonin receptor binding activity, with a chelating moiety L for attaching the metal-radiomnuclide; and particularly
- 10 - the use of a well-defined spacing group A and a secondary or tertiary nitrogen atom (symbol B), both essential elements in improving the desired receptor binding affinity.

15 In the above labelled substances of the invention the symbol A is preferably an alkane, alkoxyalkane or alkylthioalkane biradical having 1 to 6 carbon atoms, a cycloalkylene group having 5 or 6 carbon atoms, or an (alkyl)cycloalkane biradical having 6 to 8 carbon atoms; and E is preferably selected from the following groups:

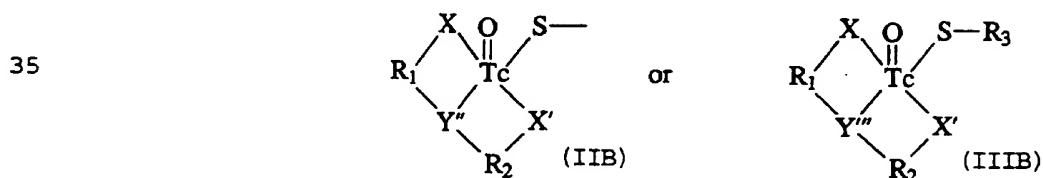
20 Ar"-C(=T)<sub>r</sub>-(CH<sub>2</sub>)<sub>p</sub>-, Ar"-O-(CH<sub>2</sub>)<sub>q</sub>- or Ar"-S-(CH<sub>2</sub>)<sub>q</sub>-

wherein:

- p is an integer from 0 to 4;
- q is an integer from 0 to 3;
- 25 r is an integer from 0 to 1;
- T is O or H<sub>2</sub>; and
- Ar" is a phenyl group, optionally substituted with one or more substituents selected from the group consisting of halogen, trifluoromethyl, (C<sub>1</sub>-C<sub>4</sub>)alkyl and (C<sub>1</sub>-C<sub>4</sub>)alkoxy.

30

Preferred chelating group L in the above labelled substances is a metal labelled chelating moiety with the general formula



wherein:

X and X' are each individually O or S;

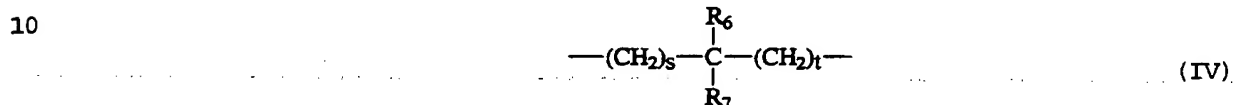
Y" is S or NR<sub>4</sub>",

wherein R<sub>4</sub>" is a hydrogen atom or a (C<sub>1</sub>-C<sub>4</sub>)alkyl group;

5 Y'" is NR<sub>4</sub>' ,

wherein R<sub>4</sub>' is a covalent bond to A;

R<sub>1</sub> and R<sub>2</sub> are each independently a biradical of the general formula



wherein:

15 R<sub>6</sub> and R<sub>7</sub> are each individually selected from the group consisting of hydrogen, methyl, and fluoro, or wherein R<sub>6</sub> and R<sub>7</sub> together constitute an oxo group; and

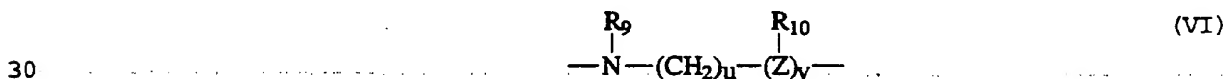
s and t are each individually 0, 1 or 2, with the proviso that s and t together are 1 or 2

20 R<sub>3</sub> is a substituent selected from the group consisting of substituted or unsubstituted (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, and aryl, wherein the substituents are selected from the group consisting of (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, halogen and trifluoromethyl;

Tc is <sup>99m</sup>Tc.

25

Preferred group B in the above labelled substances of the invention is a group of the general formula



wherein:

Z is CH or N;

R<sub>9</sub> and R<sub>10</sub> are each individually H or (C<sub>1</sub>-C<sub>3</sub>)alkyl, or R<sub>9</sub> and R<sub>10</sub> form together a biradical of the formula

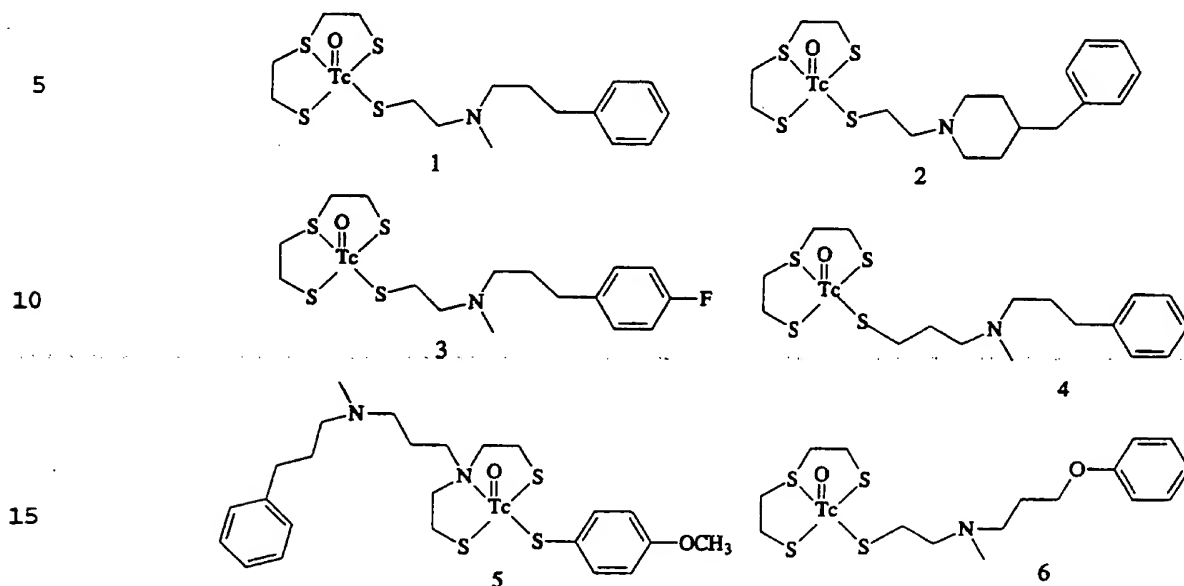
35 -CH<sub>2</sub>-CH<sub>2</sub>-;

u is an integer from 0 to 2;

v is an integer from 0 to 1.



Suitable examples of the zero-charged  $^{99m}\text{Tc}$  - labelled substances according to the invention are:



The above labelled substances of the invention have been tested in a suitable model experiment that is predictive for in vivo application. This experiment is described in the Examples. From the results of this experiment it will be evident, that the labelled substances of the present invention have properties which make them suitable for the intended use.

The new  $^{99m}\text{Tc}$  - labelled substances of the invention can be prepared in a manner known per se for related compounds. For this purpose (a) a compound of the general formula



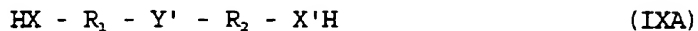
wherein the symbols A, B and E have the meanings given hereinbefore, is reacted with technetium-99m in the form of a salt, if necessary in the presence of a reducing agent, or of a chelate bound to a comparatively weak chelator, in the presence of a tridentate coligand of the general formula



wherein the symbols have the meaning given hereinbefore,  
or (b) a compound of the general formula



wherein  $L''$  is a tridentate chelating group of the general formula

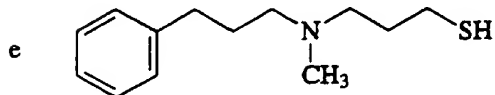
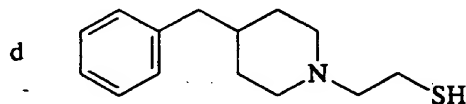
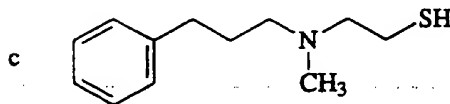
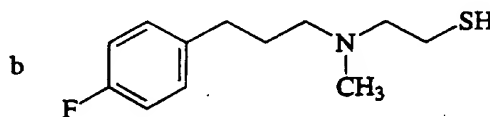
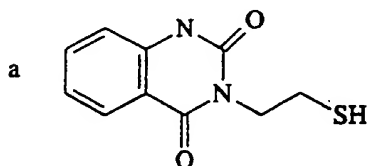


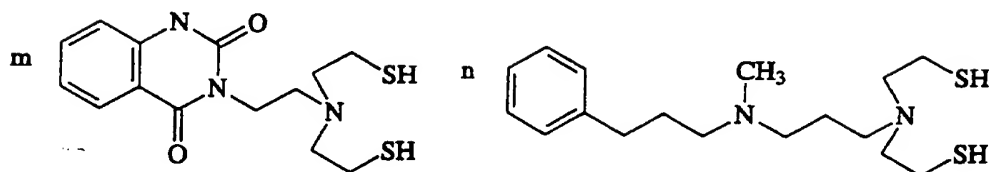
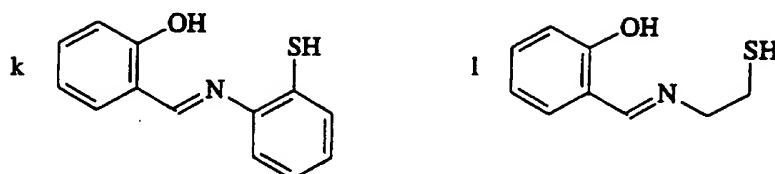
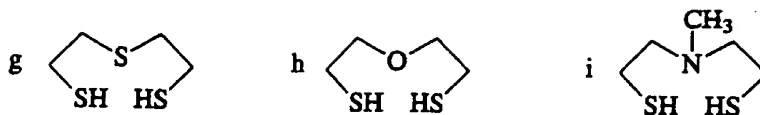
and the other symbols have the meanings given hereinbefore, is reacted with technetium-99m in the form of a salt, if necessary in the presence of a reducing agent, or of a chelate bound to a comparatively weak chelator, in the presence of a monodentate coligand of the general formula



wherein  $R_3$  has the meaning given hereinbefore.

Suitable examples of monodentate ligands of the general formula VII are represented by the formulas a to e below. These ligands can be combined, for example, with the coligands g to n:





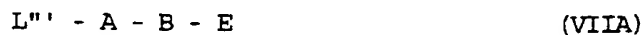
A suitable example of a tridentate ligand of the general formula VIIA is the above ligand of formula m.

As indicated above, it is beyond expectation that in the latter-mentioned complex formation, wherein a tridentate/monodentate ligand combination is involved, the reaction proceeds so selectively to the desired substance, without the formation of by-products, wherein more than one monodentate ligand or more than one tridentate ligand are involved in the chelation of a technetium-99m ion.

The present invention also relates to new ligands for chelating metal atoms, having the general formulas:



and



wherein:

L'' is a tridentate chelating group, as defined hereinbefore;

A, B and E have the meanings given hereinbefore, with the proviso that in compound VII B is not an NH group when E is (C<sub>3</sub>)alkyl phenyl.

5       The invention further relates to a radiopharmaceutical composition, comprising in addition to a pharmaceutically acceptable carrier material and, if desired, at least one pharmaceutically acceptable adjuvant, as the active substance a labelled substance as defined above.

10       The invention also relates to a method for detecting and localizing tissues having serotonin receptors in the body of a warm-blooded living being, in particular in the brain of said being, which comprises (i) administering to said being a composition comprising, in a quantity sufficient for external imaging, a <sup>99m</sup>Tc - labelled substance as defined  
15       above, and thereupon (ii) subjecting said being to external imaging to determine the targeted sites in the body of said being in relation to the background activity. The method is especially useful to detect and localize tissues having serotonin receptors of the 5-HT<sub>2A</sub> type.

20       It is frequently not desirable to put the ready-for-use composition at the disposal of the user, in connection with the often poor shelf life of the radiolabelled substance and/or the short half-life of the radionuclide used. In such cases the user will perform the labelling reaction with the radionuclide in the clinical hospital or laboratory.  
25       For this purpose the various reaction ingredients are then offered to the user in the form of a so-called cold "kit". It will be obvious that the manipulations necessary to perform the desired reaction should be as simple as possible to enable the user to prepare from the kit the radioactive labelled composition by using the facilities that are at  
30       his/her disposal. Therefore the invention also relates to a kit for preparing a radiopharmaceutical composition.

35       Such a kit according to the present invention may comprise (i) a serotonin receptor binding compound having the general formula VII together with a tridentate ligand of the general formula IX, or a serotonin receptor binding compound of the general formula VIIA together with a monodentate ligand of the general formula VIIIA, to which

compounds, if desired, an inert pharmaceutically acceptable carrier and/or formulating agents and/or adjuvants is/are added, (ii) a reducing agent, and, if desired, a chelator, said ingredients (i) and (ii) optionally being combined, and (iii) instructions for use with a prescription for reacting the ingredients of the kit with  $^{99m}\text{Tc}$  in the form of a pertechnetate solution.

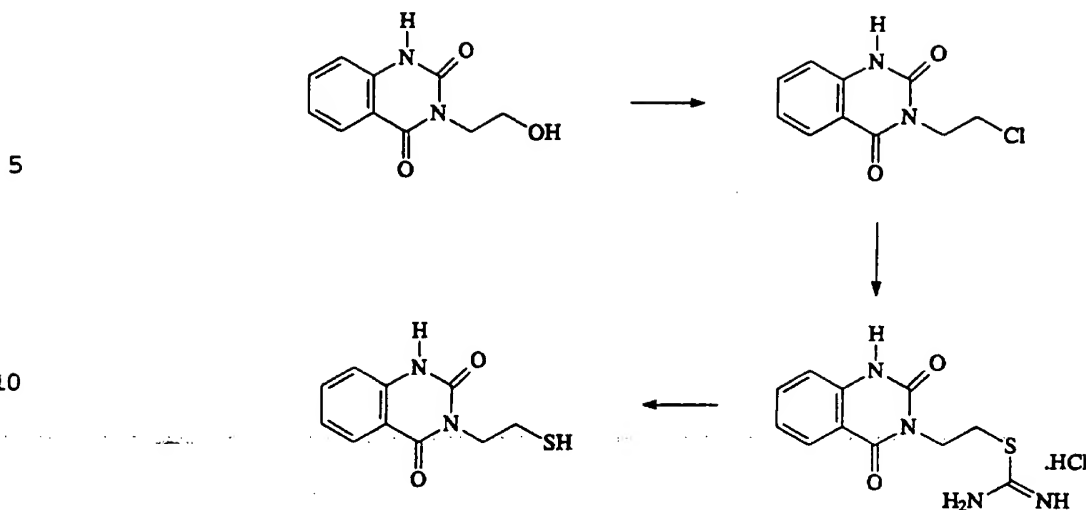
The radionuclide  $^{99m}\text{Tc}$  will preferably be added separately in the form of a pertechnetate solution. In that case the kit will comprise a suitable reducing agent and, if desired, a chelator, the former to reduce the pertechnetate or the perrhenate. As a reducing agent may be used, for example, a dithionite or a metallic reducing agent. The ingredients may optionally be combined, provided they are compatible. Such a monocomponent kit, in which the combined ingredients are preferably lyophilized, is excellently suitable for being reacted, by the user, with the radionuclide solution. As a reducing agent for the above-mentioned kits is preferably used a metallic reducing agent, for example,  $\text{Sn(II)}$ ,  $\text{Ce(III)}$ ,  $\text{Fe(II)}$ ,  $\text{Cu(I)}$ ,  $\text{Ti(III)}$  or  $\text{Sb(III)}$ ;  $\text{Sn(II)}$  is excellently suitable. The receptor binding compound of the above-mentioned kits may be supplied as a solution, for example, in the form of a physiological saline solution, or in some buffer solution, but is preferably present in a dry condition, for example, in the lyophilized condition. When used as a component for an injection liquid it should be sterile, in which, when the constituent is in the dry state, the user should preferably use a sterile physiological saline solution as a solvent. If desired, the above-mentioned constituent may be stabilized in the conventional manner with suitable stabilizers, for example, ascorbic acid, gentisic acid or salts of these acids, or it may comprise other auxiliary agents, for example, fillers, such as glucose, lactose, mannitol, and the like.

The invention will now be described in greater detail with reference to the following specific Examples.

#### Example I

Synthesis of the above-defined ligand a: 3-(2-mercaptoethyl)-2,4-(1H,3H)-quinazolindione

12



Starting from 3-(2-hydroxyethyl)-2,4-(1H,3H)-quinazolin-2(1H)-one, which is obtained from methylantranilate (R.J. Grout, M.W. Partridge, J. Chem. Soc. 1960, 3546-3550) the monodentate ligand **a** is prepared in three steps following a procedure described in DD 298783. The compound **a** is obtained as a white powder with a m.p. of 189.5-191°C (lit. 192.5-194.5°C).

#### Example II

Synthesis of the above-defined ligand **c**: N-2-mercaptoethyl-N-methyl-3-phenylpropylamine.

##### (a). N-2-hydroxyethyl-N-methyl-3-phenylpropylamine.

To a mixture of N-methylaminoethanol (22.5 g; 0.3 mol) with n-butanol (60 ml) is added powdered  $K_2CO_3$  (36 g; 0.26 mol). The suspension is heated to 95°C and then a mixture of 3-phenylpropylchloride (38.7 g; 0.25 mol) with n-butanol (25 ml) is added during 2 h.

The resultant reaction mixture is stirred at 100-106°C for 2 h. After cooling to ambient temperature, the solid is removed by filtration. The filtrate is evaporated in vacuo to provide a viscous oil which after fractional distillation yields 36.7 g (76%) of the title product as a colourless oil; b.p. 93-94°C/12Pa;  $n_D^{21} = 1.5217$ . The product is identified by  $^1H$ -NMR.

(b). N-2-mercaptoethyl-N-methyl-3-phenylpropylamine.

To a solution of the above-prepared N-hydroxyethyl-N-methyl-3-phenylpropylamine (9.66 g; 50 mmol) in methylene chloride (50 ml) is added a solution of HCl in diethyl ether (26.5%; 9.63 g; 70 mmol). The resultant homogeneous mixture is cooled to -20°C, and thionylchloride (8.3 g; 70 mmol) is added in one portion. The mixture is allowed to reach room temperature and is then refluxed for 5 h. The solvent and the excess of thionylchloride are removed in vacuo to give a slightly brown solid which is used without purification.

If desired, the free base can be obtained by treating the crude above product (30 mmol) with a solution of NaHCO<sub>3</sub> (5 g in 30 ml water) and extracting the resultant mixture with methylene chloride (1 x 30 ml; 2 x 20 ml). After washing (15% aqueous NaCl, 20 ml) and drying, the filtrate is evaporated to dryness, after which the residue is distilled at 40 Pa to give 5.7 g of the desired product (90%) as a slightly yellow oil. The product is identified by <sup>1</sup>H-NMR;  $n_D^{21.2} = 1.5184$ .

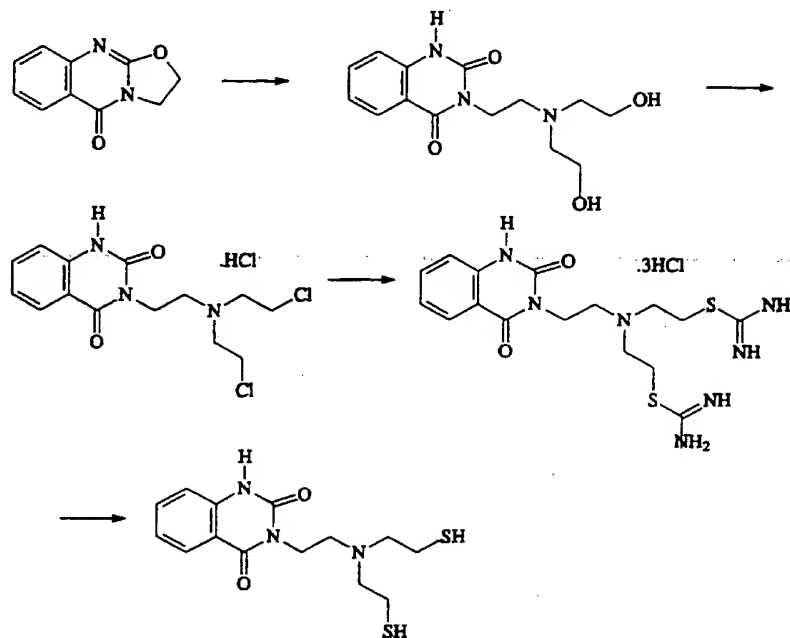
To a stirred mixture of the crude hydrochloride, as obtained above, in ethanol (45 ml) is added thiourea (4.18 g; 55 mmol). The reaction mixture is refluxed for 9 h until the starting material disappeared on TLC. After cooling to room temperature, the clear brown solution is evaporated and the viscous residue is dissolved in 50 ml water. While flushing with nitrogen, the solution is heated to 80°C; then solid sodium hydroxide (8 g, 200 mmol) is added during 5 min. The resultant biphasic system is refluxed for 3 h, and, after cooling to room temperature, neutralized by addition of solid KH<sub>2</sub>PO<sub>4</sub> to pH 8-9. Extraction with methyl-tert.butylether (3 x 25 ml), followed by washing (satd. aqueous NaCl, 20 ml) and drying, affords a yellow coloured solution which is concentrated in vacuo. The oily residue is finally purified by short-path distillation at 40 Pa, to yield the desired title compound in a yield of 3.84 g (37%) as a colourless liquid;  $n_D^{22.5} = 1.5379$ .

<sup>1</sup>H-NMR (90 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 1.84 [m, 2H, Ph-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-N]; 2.23 [s, 3H, N-CH<sub>3</sub>]; 2.30 - 2.80 [m, 8H, Ph-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-N(CH<sub>3</sub>)-CH<sub>2</sub>-CH<sub>2</sub>-]; 7.21 [m, 5H, Ar-H].

In a corresponding manner ligands **b**, **d** and **e** are prepared.

**Example III**

Synthesis of the above defined ligand **m**: 3-[2-(N,N-bis-2-mercaptoethyl)aminoethyl]-2,4-1H,3H-quinazolinedione.



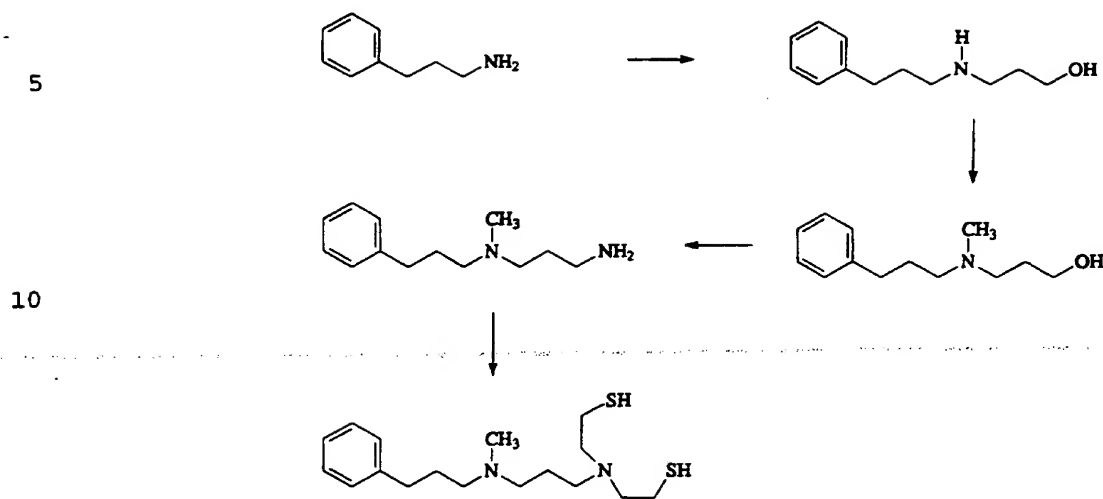
2,3-Dihydro-5H-oxazolo[2,3b]-5-quinazolinone is prepared according to Grout and Partridge (J. Chem. Soc. 1960, 3546).

This product (4.7 g) is converted with diethanolamine (3.15 g) in 50 ml of toluene as the solvent in an autoclave at 155°C within 6 h to 3-[2-(N,N-bis-2-hydroxyethyl)aminoethyl]-2,4-1H,3H-quinazolinedione in a yield of 81%. The diol obtained is thereupon converted with thionylchloride (50 g) to the corresponding chloramine-bis(hydrochloride) (yield 100%). This compound is converted in 74% to the corresponding bis(isothiuronium)salt by heating with thiourea (3.85 g) in methoxyethanol during 2 hours. Saponification with aqueous sodium hydroxide produces the desired title ligand in a yield of 25%.

**Example IV**

Synthesis of the above-defined ligand **n**: N-3[2(N,N-bis-2-mercaptoethyl)]-aminopropyl-N-methyl-3-phenylpropylamine





(a). **N-(3-hydroxypropyl)-3-phenylpropylamine**

To a suspension of potassium carbonate (41.5 g, 0.3 mol) in n-butanol (250) is added 3-aminopropanol (42.1 g, 0.56 mol). The mixture is heated to 105-110°C, and then a mixture of 3-phenylpropylchloride (43.2g, 0.28 mol) with n-butanol (40 ml) is added during 3 hours. The resultant reaction mixture is refluxed for 4 hours.

After cooling to ambient temperature (22°C) the solid is removed by filtration and washed with CHCl<sub>3</sub> (2 x 60 ml). The filtrate is evaporated to give an oil which is fractionally distilled to yield 39.6 g (73%) N-(3-hydroxypropyl)-3-phenylpropylamine as a low melting solid; bp. 114-115°C/18 Pa; m.p. 37°C.

(b) **N-(3-hydroxypropyl)-N-methyl-3-phenylpropylamine**

N-(3-hydroxypropyl)-3-phenylpropylamine (23.2 g, 0.12 mol) is dissolved in formic acid (85%; 33g, 0.6 mol). To the slightly yellow colored mixture an aqueous solution of formaldehyde (36%; 11.2 ml, 0.144 mol) is added.

The whole is heated under stirring at 100 - 110°C. After 8 hours, (meanwhile the evolution of CO<sub>2</sub> has ceased) the mixture is cooled and concentrated in vacuo at 50°C.

The residue is acidified with HCl (2N, 30 ml) and after standing at 22°C for 3 days, NaOH (25%, 50 ml) is added to the homogeneous mixture. The

oil formed is extracted with MTBE (2 x 60 ml) and dried over NaOH pellets. The solvent is evaporated and the remaining product purified by fractional distillation to give 22.5 g (90%) N-(3-hydroxypropyl)-N-methyl-3-phenylpropylamine as a colorless viscous liquid; bp. 102 - 103°/12 Pa (Lit: 147.5°C/5 Torr).

The diamine is prepared by amination of the chloro intermediate using the sodium diformylamide method described by Yinglen and Hongwen (Synthesis 1990, 112 - 124).

(c). N-(3-aminopropyl)-N-methyl-3-phenylpropylamine

To a solution of N-(hydroxypropyl)-N-methyl-3-phenylpropylamine (12.4 g; 60 mmol) in chloroform (50 ml) an etherical solution of hydrogen chloride (22%, 13.2 g, 80 mmol) is added. The resultant homogeneous mixture is cooled to -20°C and thionylchloride (10 g, 84 mmol) is added in one portion. The mixture is allowed to warm to room temperature and then refluxed for 3 - 5 h. The solvent and the excess of thionylchloride are removed in vacuo to give a slightly brown solid which is used without purification.

The free base is obtained by treating the crude product with a solution of NaHCO<sub>3</sub> (8 g in 40 ml water) and extracting the resultant mixture with chloroform (1 x 35 ml, 2 x 20 ml). After washing (15% NaCl, 20 ml) and drying (MgSO<sub>4</sub>) the filtrate is evaporated and the residue is distilled at 40 Pa to give 12.5 of slightly yellow oil.

A mixture of this chloro derivative (12.4 g, 55.2 mmol), sodium diformylamide (6.3 g, 66.3 mmol) and dry DMF (20 ml) is stirred at 120 - 125°C for 7 hours. After cooling to ambient temperature the solid is removed by filtration and washed with CHCl<sub>3</sub> (2 x 10 ml). The combined filtrate is evaporated and the residue is dissolved in 4 N HCl (40 ml). The homogenous mixture is refluxed for 2 hours and evaporated to near dryness. The residue is treated with 25 % NaOH (40 ml) and the free alkylamine liberated is extracted with MTBE (3 x 25ml). The combined extract is dried (NaOH) and evaporated. The crude product obtained is purified by distillation to give 10.2 g (82.1% overall yield); b.p. 74-75°C/9 Pa,  $n_{D}^{22.0} = 1.5160$  (Lit. US 3,211,789; C.A. 1966, 64, 5011e.; b.p. 154 - 6°C/10 torr,  $n_{D}^{20.0} = 1.15140$ ).

(d). N-3-[2-(N,N-bis-2-mercaptoethyl)]-aminopropyl-N-methyl-3-phenylpropylamine **n**

The final product is prepared according to J.L. Corbin et al. (Inorg. Chim. Acta 90 (1984) 41-51).

5 A solution of N-(3-aminopropyl)-N-methyl-3-phenylpropylamine (2g, 0.01 mol) in 40 ml of dry toluene is mixed with a solution of ethylene sulfide (1.3g, 0.021 mol) in 30 ml of dry toluene and allowed to stand overnight (sealed tube, argon flushed). The reaction mixture is heated to 130°C (bath temperature) for 15 h, cooled, and filtered to removed a  
10 small amount of polymer product. The solvent is removed and the crude product precipitated as hydrochloride. Recrystallization from methanol/diethyl ether yields **n** as a white powder.

#### 15 Example V

##### Labelling procedure.

A vial containing a lyophilized mixture of 100 mg sodium gluconate and 0.5 mg of SnCl<sub>2</sub> is reconstituted with a mixture of 3ml of water and 0.5  
20 mg of <sup>99m</sup>Tc-pertechnetate (ca. 500 MBq). The resulting <sup>99m</sup>Tc-gluconate complex is added to 1 ml of an acetonitrilic solution containing equimolar amounts of the tridentate ligand **g** (0.015 mmol) and the monodentate ligand **c** (0.015 mmol). After agitating the mixture for 20 minutes, the pH is adjusted to approximately 9 with 0.1 N NaOH. Then the  
25 aqueous solution is extracted with 1 ml of diethyl ether. About 90% of the activity is recovered. The organic phase is washed twice with 1 ml of water and dried over Na<sub>2</sub>SO<sub>4</sub>.

For biochemical studies the solvent is carefully evaporated and the residue is redissolved in DMSO. The labelled substance **1**, as shown  
30 hereinbefore, is obtained.

In a corresponding manner the labelled substances **2**, **3** and **4** are obtained, using tridentate ligand **g** in combination with monodentate ligands **d**, **b** and **e**, respectively, as the starting compounds. The same procedure applies for technetium complex **5**, using the tridentate ligand  
35 **n** in combination with a monodentate thiol, e.g. 4-methoxybenzenthionol.

Example VI

## Biochemical studies.

5 The quantitative binding characteristics in vitro are determined with the aid of inhibition experiments. Substances 1-6 mentioned above are used.

10 The cortex of rat brain is homogenized in 10 volumes of ice-cold Tris-buffer solution (50 mM Tris-HCl, pH 7.6) with an Ultra-Turrax<sup>®</sup> T25 homogenizer. The homogenate is centrifuged at 20,000 g for 10 min. The resulting pellet is resuspended with the Ultra-Turrax and centrifuged again at 20,000 g for 10 min. After repeating the same procedure, the pellet is resuspended in 10 volumes of buffer and stored at -20°C until use in the binding studies.

15 The time dependency of ketanserin binding is studied on these membrane preparations (0.013 mg/ml protein). The samples are incubated at 23°C for various times with ketanserin hydrochloride [ethylene-<sup>3</sup>H] (2356.9 GBq/mmol) in the presence and absence of 1  $\mu$ M unlabelled mianserin, a well-known serotonin receptor antagonist just as ketanserin. For inhibition studies the samples are incubated at 23°C for 60 min. The binding assays are terminated by rapid filtration through GF/B glass fiber filters. The filters are rapidly washed with four 4-ml portions of ice-cold buffer, transferred to 10 ml of scintillation fluid (Ultima-Gold<sup>®</sup>) and analysed for radioactivity. Aliquots of the incubation fluid are measured as well. Corrections are made for binding <sup>3</sup>H-ketanserin to the filters. The protein content of the membrane suspensions is estimated according to the method of Lowry et al. (J. Biol. Chem. 1951, 25 193, 265).

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## Results:

	Substance	IC <sub>50</sub> (nM) (5-HT <sub>2A</sub> )
5	1	52 ± 9
	2	22 ± 3
	3	65 ± 3
	4	7 ± 2
	5	95 ± 17
	6	12 ± 3
10	ketanserin	5
	serotonin	638

## Conclusion:

15 The binding studies show that the binding constants of substances 1-6 are of the same order of magnitude as the binding constant of ketanserin, and are therefor promising metal-labelled compounds for imaging.

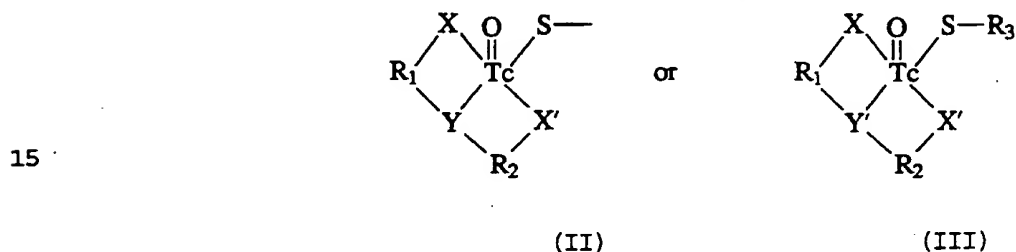
## Claims

1. A zero-charged  $^{99m}\text{Tc}$  - labelled substance having a serotonin receptor binding activity, wherein the serotonin receptor binding compound is represented by the general formula



wherein:

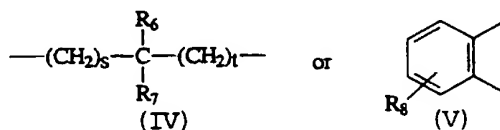
- 10 L is a metal labelled chelating moiety with the general formula



wherein:

- 20 X and X' are each individually O or S;  
 Y is O, S, Se,  $\text{NR}_4$ ,  $\text{PR}_4$  or  $-\text{C}(\text{R}_4)=\text{N}-$ ,  
 wherein  $\text{R}_4$  is a hydrogen atom or a  $(\text{C}_1-\text{C}_6)$ alkyl group, optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, oxo, [N-mono- or N,N-di $(\text{C}_1-\text{C}_3)$ alkyl]-amino,  $(\text{C}_1-\text{C}_3)$ alkyl,  $(\text{C}_1-\text{C}_3)$ alkoxy and optionally substituted phenyl;  
 25 Y' is  $\text{NR}_4'$  or  $\text{PR}_4'$  or  $-\text{C}(\text{R}_4')=\text{N}-$ ,  
 wherein  $\text{R}_4'$  is a covalent bond to A;  
 $\text{R}_1$  and  $\text{R}_2$  are each independently a biradical of the general formula

30



35

wherein:

- $\text{R}_6$ ,  $\text{R}_7$  or  $\text{R}_8$  are each individually selected from the group consisting of hydrogen,  $(\text{C}_1-\text{C}_3)$ alkyl,  $(\text{C}_1-$

C<sub>3</sub>)alkoxy and fluoro, or wherein R<sub>6</sub> and R<sub>7</sub> together constitute an oxo group; and

s and t are each individually 0, 1 or 2, with the proviso that s and t together are 1 or 2;

R<sub>3</sub> is a substituent selected from the group consisting of substituted or unsubstituted (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, and phenyl, wherein the substituents are selected from the group consisting of (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, halogen and trifluoromethyl;

Tc is <sup>99m</sup>Tc;

A is a 2- to 8-membered hydrocarbon biradical, wherein the carbon atoms may be interrupted by one or two heteroatoms selected from O and S;

B is an N-(C<sub>1</sub>-C<sub>4</sub>)alkyl group, an NH group, or an optionally substituted piperidin-derived, piperazin-derived, morpholin-derived or pyrrolidin-derived biradical; and

E is selected from the following groups:

Ar-C(=T)<sub>r</sub>-(CH<sub>2</sub>)<sub>p</sub>-, Ar-O-(CH<sub>2</sub>)<sub>q</sub>-, Ar-S-(CH<sub>2</sub>)<sub>q</sub>-, Ar-C(Ar')-C(=T)<sub>r</sub>-(CH<sub>2</sub>)<sub>p</sub>- and Ar-C(Ar')=,

wherein:

p is an integer from 0 to 4;

q is an integer from 0 to 3;

r is an integer from 0 to 1;

T is O or H<sub>2</sub>; and

Ar and Ar' are each independently unsubstituted or substituted aryl or heteroaryl groups, wherein the aryl or heteroaryl groups are selected from phenyl, pyridyl, pyrrolyl, triazinyl, pyridazinyl, imidazolyl, pyrazolyl, pyrazinyl, pyrimidinyl, indolyl, isoindolyl, indazolyl, benzofuranyl and benzisoxazolyl, and wherein the substituents are selected from halogen, trifluoromethyl, (C<sub>1</sub>-C<sub>4</sub>)alkyl and (C<sub>1</sub>-C<sub>4</sub>)alkoxy;

or wherein E together with B constitutes an optionally substituted 2,4-dihydroquinazolyl group attached with its (3-N)atom to A.

2. A labelled substance as claimed in claim 1, wherein the serotonin receptor binding compound has the general formula



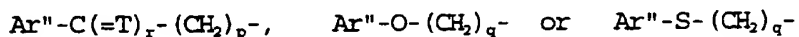
5 wherein:

L and B have the meanings given in claim 1;

A' is an alkane, alkoxyalkane or alkylthioalkane biradical having 1 to 6 carbon atoms, a cycloalkylene group having 5 or 6 carbon atoms, or an (alkyl)cycloalkane biradical having 6 to 8 carbon atoms; and

10

E' is selected from the following groups:



15

wherein:

p is an integer from 0 to 4;

q is an integer from 0 to 3;

r is an integer from 0 to 1;

T is O or H<sub>2</sub>; and

20

Ar'' is a phenyl group, optionally substituted with one or more substituents selected from the group consisting of halogen, trifluoromethyl, (C<sub>1</sub>-C<sub>4</sub>)alkyl and (C<sub>1</sub>-C<sub>4</sub>)alkoxy.

3. A labelled substance as claimed in claim 2, wherein the serotonin receptor binding compound has the general formula

25



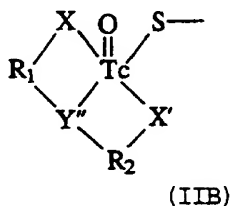
wherein:

30

A' and E' have the meanings given in claim 2;

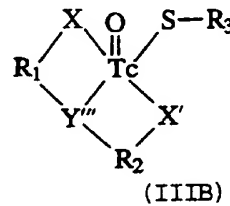
L' is a metal labelled chelating moiety with the general formula

35



(IIB)

or



(IIIB)



wherein:

X and X' are each individually O or S;

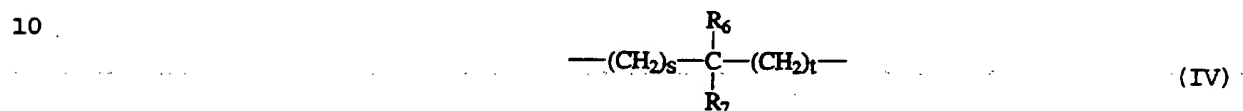
Y" is S or NR<sub>4</sub>"

wherein R<sub>4</sub>" is a hydrogen atom or a (C<sub>1</sub>-C<sub>4</sub>)alkyl group;

5 Y'" is NR<sub>4</sub>' ,

wherein R<sub>4</sub>' is a covalent bond to A;

R<sub>1</sub> and R<sub>2</sub> are each independently a biradical of the general formula



wherein:

15 R<sub>6</sub> and R<sub>7</sub> are each individually selected from the group consisting of hydrogen, methyl, and fluoro, or wherein R<sub>6</sub> and R<sub>7</sub> together constitute an oxo group; and

s and t are each individually 0, 1 or 2, with the proviso that s and t together are 1 or 2

20 R<sub>3</sub> is a substituent selected from the group consisting of substituted or unsubstituted (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, and aryl, wherein the substituents are selected from the group consisting of (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, halogen and trifluoromethyl;

Tc is <sup>99m</sup>Tc;

25 B' is a group of the general formula



wherein:

30 Z is CH or N;

R<sub>9</sub> and R<sub>10</sub> are each individually H or (C<sub>1</sub>-C<sub>3</sub>)alkyl, or R<sub>9</sub> and R<sub>10</sub> form together a biradical of the formula -CH<sub>2</sub>-CH<sub>2</sub>-;

u is an integer from 0 to 2;

35 v is an integer from 0 to 1.

4. A method of preparing a  $^{99m}\text{Tc}$  - labelled substance as claimed in claim 1, characterized in that (a) a compound of the general formula



5

wherein the symbols A, B and E have the meanings given in claim 1, is reacted with technetium-99m in the form of a salt, if necessary in the presence of a reducing agent, or of a chelate bound to a comparatively weak chelator, in the presence of a tridentate coligand of the general formula

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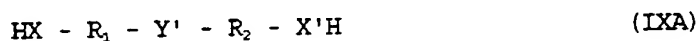
wherein the symbols have the meaning given in claim 1,  
or (b) a compound of the general formula

15



wherein  $\text{L}''$  is a tridentate chelating group of the general formula

20



and the other symbols have the meanings given in claim 1, is reacted with technetium-99m in the form of a salt, if necessary in the presence of a reducing agent, or of a chelate bound to a comparatively weak chelator, in the presence of a monodentate coligand of the general formula

25



30

wherein  $\text{R}_3$  has the meaning given in claim 1.

5. A compound to be used for the method according to claim 4, having the general formula

35



wherein the symbols have the meanings given in claim 1, with the proviso that B is not an NH group when E is (C<sub>1</sub>)alkyl phenyl.

5 6. A compound to be used for the method according to claim 5, having the general formula



wherein the L'' has the meaning given in claim 4 and the other symbols have the meanings given in claim 1.

10

7. A radiopharmaceutical composition, comprising in addition to a pharmaceutically acceptable carrier material and, if desired, at least one pharmaceutically acceptable adjuvant, as the active substance a labelled substance as claimed in claim 1, 2 or 3.

15

8. A method for detecting and localizing tissues having serotonin receptors in the body of a warm-blooded living being, in particular in the brain of said being, which comprises (i) administering to said being a composition comprising, in a quantity sufficient for external imaging, a <sup>99m</sup>Tc - labelled substance as claimed in claim 1, 2 or 3, and thereupon (ii) subjecting said being to external imaging to determine the targeted sites in the body of said being in relation to the background activity.

20

9. A method according to claim 8, characterized in that said serotonin receptors are of the 5-HT<sub>2A</sub> type.

25

10. A kit for preparing a radiopharmaceutical composition, comprising (i) a serotonin receptor binding compound having the general formula VII together with a tridentate ligand of the general formula IX, or a serotonin receptor binding compound of the general formula VIIA together with a monodentate ligand of the general formula VIIIA, to which compounds, if desired, an inert pharmaceutically acceptable carrier and/or formulating agents and/or adjuvants is/are added, (ii) a reducing agent, and, if desired, a chelator, said ingredients (i) and (ii) optionally being combined, and (iii) instructions for use with a prescription for reacting the ingredients of the kit with <sup>99m</sup>Tc in the form of a pertechnetate solution.

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35

**Abstract**

The invention relates to a zero-charged  $^{99m}\text{Tc}$  - labelled substance having a serotonin receptor binding activity, wherein the serotonin receptor binding compound is represented by the general formula



wherein:

10 L is a chelating moiety selected consisting of a tridentate/monodentate chelating combination;

A is a 2- to 8-membered hydrocarbon biradical, wherein the carbon atoms may be interrupted by one or two heteroatoms selected from O and S;

15 B is an N-(C<sub>1</sub>-C<sub>4</sub>)alkyl group, an NH group, or an optionally substituted piperidin-derived, piperazin-derived, morpholin-derived or pyrrolidin-derived biradical; and

E is selected from the following groups:

20 Ar-C(=T)<sub>r</sub>-(CH<sub>2</sub>)<sub>p</sub>-, Ar-O-(CH<sub>2</sub>)<sub>q</sub>-, Ar-S-(CH<sub>2</sub>)<sub>q</sub>-, Ar-C(Ar')-C(=T)<sub>r</sub>-(CH<sub>2</sub>)<sub>p</sub>- and Ar-C(Ar')=,

wherein:

p is an integer from 0 to 4;

25 q is an integer from 0 to 3;

r is an integer from 0 to 1;

T is O or H<sub>2</sub>; and

30 Ar and Ar' are each independently unsubstituted or substituted aryl or heteroaryl groups, wherein the aryl or heteroaryl groups are selected from phenyl, pyridyl, pyrrolyl, triazinyl, pyridazinyl, imidazolyl, pyrazolyl, pyrazinyl, pyrimidinyl, indolyl, isoindolyl, indazolyl, benzofuranyl and benzisoxazolyl, and wherein the substituents are selected from halogen, trifluoromethyl, (C<sub>1</sub>-C<sub>4</sub>)alkyl and (C<sub>1</sub>-C<sub>4</sub>)alkoxy;

35 or wherein E together with B constitutes an optionally substituted 2,4-dihydroquinazolyl group attached with its (3-N)atom to A.

wherein said serotonin receptor binding compound is labelled with

technetium-99m in the form of oxotechnetium(V), said technetium being attached to said compound by means of said chelating moiety.

5 The invention also relates to a method of preparation of said labelled substance, a radiopharmaceutical composition comprising said labelled substance, a method for detecting and localizing tissues having serotonin receptors with the aid of said labelled substance and a kit for preparing a radiopharmaceutical composition containing said labelled substance.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US96/04239

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 51/04; C07F 13/00

US CL : 534/14; 424/1.65

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 534/14; 424/1.65

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
NONEElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
CAS ONLINE-structure search on STN

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 5,382,654 (LYLE ET AL.) 17 January 1995, columns 4-7.	1-10
A	US, A, 5,075,099 (SRINIVASAN ET AL.) 24 December 1991, columns 2-3.	1-10
A	US, A, 4,957,728 (DEUTSCH ET AL.) 18 September 1990, column 2.	1-10
A	US, A, 4,980,147 (FRITZBERG ET AL.) 25 December 1990, columns 5-6.	1-10
Y	DE, A, 279,023 (SPIES ET AL.) 23 May 1990, pages 1-3, especially page 1.	1-10

☒ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	*T	Later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US96/04239

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Magnetic Resonance in Chemistry, Volume 32, issued 1994, C. I. Stassinopoulou et al., "1H and 13C NMR Structural Studies in Solution of Oxotechnetium(V) Complexes with N, N-Bis(2-mercaptoethyl)-N', N"-diethylenediamine and N, N-Bis(2-mercaptoethyl)-2-ethylthioethylamine", pages 532-536, especially Figure 1 on page 533.	1-10
Y	Journal of Medicinal Chemistry, Volume 37, issued 1994, Spiros G. Mastrostamatis et al., "Tridentate Ligands Containing the SNS Donor Atom Set as a Novel Backbone for the Development of Technetium Brain-Imaging Agents", pages 3212-3218, especially page 3213.	1-10
Y	Acta Cryst., Volume C48, issues 1992, G. Bandoli et al., "Structure of (Benzenethiolato)oxo[N-(2-sulfidophenyl) salicylidene-iminato(2-)-O, N, S]]technetium (V)*", pages 1422-1425, especially page 1423,	1-10
Y	Isotopenpraxis, Volume 26, issued 1990, H. Spies et al., "Lipophilic Technetium Complexes: VIII)* Preparation and Animal Studies of Oxotechnetium (V) Complexes with Tridentate/monodentate Ligand Coordination", pages 159-162, especially page 160.	1-10
Y	Appl. Radiat. Isot., Volume 41, number 2, issued 1990, H. J. Pietzsch et al., "Lipophilic Technetium Complexes-VII. Neutral Oxotechnetium (V) Complexes of Tridentate Schiff-bases Containing Monothioles as Co-ligands", pages 185-188, especially pages 186-187.	1-10
Y	Inorganica Chimica Acta, Volume 168, issued 1990, H. J. Pietzsch et al., "Lipophilic Technetium Complexes: IX. The Reduction of (3-Oxapentane-1, 5-dithiolato)-(p-carbmethoxybenzenethiolato)oxotechnetium(V) by Tertiary Phosphines" pages 7-9, especially page 8.	1-10
Y	Inorganica Chimica Acta, Volume 165, issues 1989, H. J. Pietzsch et al., "Lipophilic Technetium Complexes: VI. Neutral Oxotechnetium (V) Complexes with Monothiole/Tridentate Dithiole Coordination", pages 163-166, especially pages 163 and 166.	1-10
Y	Inorganica Chimica Acta, Volume 161, issued 1989, H. J. Pietzsch et al., "Lipophilic Technetium Complexes. V. Synthesis and Characterization of (3-Thiapentane-1,5-dithiolato) (thiophenolato) oxotechnetium (V)", pages 15-16, especially page	1-10